

Prognostic significance of APRI index and neutrophil/lymphocyte ratio in hepatocellular carcinoma patients undergoing liver transplantation

Inflamatur markers in hepatocellular cancer patients with liver transplantation

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Abstract

Aim: Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide. Liver transplantation (LT) is the only curative treatment that eliminates both the cirrhotic liver and the cancer. Our study aimed to demonstrate the ability of systemic and local inflammatory factors to predict prognosis and long-term survival outcomes for LT.

Materials and Methods: We analyzed 220 patients undergoing LT for HCC in two separate transplant centers between January 2012 and December 2024. The primary objectives were overall survival (OS), recurrence-free survival (RFS), and recurrence risk.

Results: The optimal cutoff values for neutrophil to lymphocyte ratio (NLR) and aspartate aminotransferase/platelet count ratio index (APRI) for OS and RFS were 0.451 and 0.68, respectively. We showed that the APRI > 0.68 (high) group had significantly better overall survival outcomes for RFS and OS. Borderline significance was observed in OS for the NLR > 4.51 group. In particular, tumor size and tumor number were found to be significant factors negatively affecting survival.

Discussion: We determined that a high systemic NLR level was useful for predicting OS, but this was not significant for recurrence or RFS. It is not a useful systemic inflammatory index for screening patients undergoing LT at high risk of recurrence. In our study, a high APRI score was associated with an increased mortality rate. Conversely, a high APRI score was associated with a better RFS. We found that a high APRI value was associated with a better OS.

Keywords

hepatocellular carcinoma, liver transplantation, survival, inflammatory markers

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This study was approved by the Ethics Committee of Acibadem University (Date: 2025-06-26, No:10/380)

Introduction

HCC is the sixth most common cancer worldwide. As the third most common cause of death, it continues to be an increasingly important health problem [1]. Treatment options include LT, surgical resection, and locoregional treatment modalities. LT is one of the most effective treatment modalities for patients with early-stage HCC. LT eliminates both cancer and liver disease, such as cirrhosis. Thus, important risk factors for new tumor formation are eliminated [2]. Although HCC patients who undergo LT are selected according to strict selection criteria, the recurrence rate after LT is approximately 10–20% [3]. Since this directly affects long-term outcomes, selecting patients with the best probability of survival after LT in transplantation management is extremely important for the efficient use of scarce liver donor resources. Systemic markers associated with fibrosis and inflammation must be taken into consideration in the preoperative evaluation. The importance of changes in systemic inflammation in preoperatively predicting surgical and oncological outcomes in liver cancers, including HCC, has been shown in many studies [4]. A number of inflammation-based biomarkers and biomarkers related to the degree of liver fibrosis were developed to predict prognosis [5]. One of the most frequently used tools to assess patient outcomes is NLR. High NLR levels were reported to be associated with poor prognosis in patients with HCC who underwent liver resection [6]. The influence of tumor-associated neutrophils (TANs) on tumor growth, invasion, and metastasis has been revealed [7]. In parallel, there have been significant advances in the relationship between HCC progression and the tumor microenvironment (TME). As a result, NLR has begun to be used as a useful inflammatory marker to predict HCC recurrence [8]. Furthermore, several models have been developed that predict liver fibrosis status and HCC-related outcomes, including APRI. To our knowledge, inflammatory markers associated with HCC recurrence can guide clinicians in identifying patients with poor prognosis preoperatively and postoperatively in patients undergoing LT. Numerous prognostic models for HCC have been proposed. Most of these generally incorporate clinicopathological features of the patient and tumor [9]. These models often fail to reveal the specific inflammatory factors that influence long-term outcomes. Recent studies evaluating the role of inflammatory biomarkers and markers related to liver fibrosis grade in HCC patients in the context of LT have yielded inconsistent results and remained uncertain regarding their ability to predict survival [10]. Our study aimed to demonstrate the ability of systemic and local inflammatory factors to predict prognosis and long-term survival outcomes.

Materials and Methods

For this study, patients undergoing living and deceased donor liver transplantation were recruited consecutively at two separate transplant centers between January 2012 and December 2024. During this period, a total of 1,530 patients underwent LT for any reason. Of these, 220 patients underwent LT for HCC. Inclusion criteria were those who had not received pre-LT radiotherapy or chemotherapy. The exclusion criteria were: 1) patients with concurrent tumors from other organs or metastatic liver tumors, 2) patients with other organ transplantation but missing clinical

or follow-up information, and 3) patients with mixed tumors (HCC and cholangiocarcinoma) and recurrent HCC. Ultimately, 200 patients met the inclusion criteria. The primary objectives were OS, RFS, and recurrence risk ratio. The secondary aim was to investigate the relationship between high and low APRI and NLR and demographic and tumor characteristics. Inflammatory markers NLR and APRI were analyzed using cutoff values determined based on the Receiver Operating Characteristic (ROC) curve analysis. Preoperative serum samples were collected one week before liver transplantation in patients with HCC. NLR, a marker of inflammation with demonstrated prognostic value in liver resection for HCC, and APRI, as a non-invasive liver fibrosis marker, were used: $APRI = (AST / AST \text{ upper limit of normal}) / \text{platelet count} \times 100$. Post-LT follow-up was performed every three months using contrast-enhanced computed tomography (CT), AFP. OS was defined as the time from surgery to death or loss of follow-up. RFS was defined as the time from surgery to the detection of recurrence. Post-LT immunosuppressive protocol was performed as previously determined [11].

Statistical Analysis

Data were calculated as means, medians, frequencies, and percentages. The Mann-Whitney U test and the Kruskal-Wallis test were used to compare continuous variables. The area under the ROC curve (AUC) was used to determine the optimal cutoff value for RFS and OS analyses. ROC curve analysis was employed to determine optimal cut-off values for APRI and NLR indices with respect to OS and RFS. Survival probabilities were estimated using the Kaplan-Meier method, and differences between groups were evaluated using the log-rank test. The Youden index was used to select thresholds that provided the best balance between sensitivity and specificity. All statistical analyses were performed using SPSS version 27.0.

Ethical Approval

This study was approved by the Ethics Committee of Acibadem University (Date: 2025-06-26, No:10/380).

Results

There were no differences in clinic-demographic features (Table 1). We evaluated the relationship between post-LT results and preoperative inflammatory indices (Figure 1). The optimal cutoff values for NLR and APRI for predicting postoperative OS and RFS were 0.451 and 0.68, respectively (Figure 2 a,b). Borderline significance was observed in OS for the $NLR > 4.51$ group (Figure 2 c). We analyzed also RFS for NLR (Figure 2 d). Considering the relationship between APRI and tumor characteristics well-known to be associated with disease progression, alpha-fetoprotein (AFP) levels were significantly higher in the high APRI. When prognostic indicators were analyzed, the mortality rate was significantly higher in the low APRI group (36.8% vs. 19.9%) (Figure 2 e). Interestingly, RFS was longer in the high APRI group (median: 55 months vs. 35 months) (Figure 2 f). Follow-up was significantly longer in the high APRI group (median: 64 months vs. 36 months). Kaplan-Meier analysis produced on the entire cohort showed that the high APRI group had significantly better overall survival outcomes for RFS and OS (Figure 2 e,f). In univariate Cox regression analysis, some clinical features and tumor variables

were found to be significantly associated with OS. In particular, tumor size and tumor number were found to be significant factors negatively affecting survival. MVI was also associated with a significantly increased risk of mortality. An APRI ≤ 0.68 was found to be a significant prognostic factor increasing the risk of death by approximately 2.2-fold. In the analysis for NLR, although survival was better in patients with $NLR \leq 4.51$, the difference was not significant (Table 2).

According to multivariate Cox regression analysis, only APRI ≤ 0.68 remained a significant independent factor affecting overall survival ($p = 0.023$, HR = 2.40, 95% CI: 1.130–5.081). Tumor size and tumor number, although close to the significance threshold, were not statistically significant in multivariate analysis. Similarly, MVI also lost significance in the multivariate model. Other variables were not found to be independent factors affecting OS (Table 2). The lowest p value was found for early-stage tumor differentiation, which trended toward a reduced risk of recurrence ($p = 0.060$, HR = 0.235, 95% CI: 0.052–1.062), but did not reach statistical significance (Table 2). When patient and tumor variables were compared with high and low NLR, no difference was observed in terms of gender, age, and disease etiology, while AFP and CP B and C ratios were found to be higher in high NLR. Similarly, RFS was significantly longer in high NLR. The APRI score, an indicator of fibrosis level, was significantly higher in the group with $NLR > 4.51$. This suggests that high NLR may be associated with advanced liver disease (Table 3). When disease and tumor characteristics were examined with high and low APRI, a significant association was observed between high AFP and $APRI > 0.68$. While the mortality rate was found to be lower with high APRI, RFS and recurrence-free follow-up time were observed to be significantly longer (Table3). AUC were 0.55 and 0.51 for APRI and NLR. respectively. For OS with $APRI \leq 0.68$, sensitivity was 30.4%, specificity was 84.3%, positive predictive value (PPV) was 36.8%, negative predictive value (NPV) was 80.1%, and accuracy was 71.9%. For OS with $NLR \leq 4.51$, sensitivity was 67.4%, specificity was 19.6%, PPV was 20.1%, NPV was 66.7%, and accuracy was 30.7%. In the analysis for RFS, for $APRI \leq 0.68$, sensitivity was 18.8%, specificity was 80.8%, PPV was 15.8%, NPV was 83.9% and accuracy rate was 70.9%; for $NLR \leq 4.51$, sensitivity was 78.1%, specificity was 22.8%, PPV was 16.2%, NPV was 84.4% and accuracy rate was 31.7%.

Discussion

We also aimed to explore the association of APRI and NLR with OS and RFS in the patients with HCC after LT. We determined that a high systemic NLR level was useful for predicting OS, but this was not significant for recurrence or RFS. It is not a useful systemic inflammatory index for screening patients undergoing LT at high risk of recurrence. In our study, a low APRI score was associated with an increased mortality rate. Conversely, a high APRI score was associated with a better RFS. The time to recurrence was not different between high and low scores. We found that a high APRI value was associated with a better OS. This is inconsistent with other studies showing an association between high APRI and shorter OS [12]. However, the results of the analysis for sensitivity, specificity, PPV, and NPV showed that APRI provided high specificity and acceptable accuracy in

predicting mortality, but had limited screening power due to its low sensitivity. Based on these results, we demonstrated that while NLR has high sensitivity for mortality, its discriminatory power is limited due to very low specificity and low accuracy. Analysis of tumor recurrence revealed that although APRI has relatively higher specificity, its sensitivity remained low, while NLR, despite its high sensitivity, has low specificity and accuracy. Overall, we can suggest that while APRI and NLR provide some

Table 1. Demographic and baseline characteristics of the total cohort

Gender n (%)	
male	166 (83.0%)
female	34 (17.0%)
Age median (IQR)	66.24 (59.40-71.34)
BMI median (IQR)	26.00 (24.00-29.00)
Diagnosis n (%)	
HBV	113 (56.5%)
cryptogenic	30 (15.0%)
HCV	26 (13.0%)
ethanol	11 (6.5%)
Nash	7 (3.5%)
budd-chiari	3 (1.5%)
wilson	2 (1.0%)
autoimmune	2 (1.0%)
HCC	2 (1.0%)
cholestasis	1 (0.5%)
hemochromatosis	1 (0.5%)
Child-pugh n (%)	
A	94 (47.0%)
B	94 (47.0%)
C	12 (6.0%)
Meld median (IQR)	11.50 (8.00-17.00)
Afp median (IQR)	8.30 (3.58-49.50)
Tumor size(mm) median (IQR)	25.00 (16.00-40.00)
Number of hcc lesions median (IQR)	2.00 (1.00-3.00)
Locoregional treatment n (%)	
No	135 (67.5%)
Yes	65 (32.5%)
Mortality n (%)	
No	154 (77.0%)
Yes	46 (23.0%)
Tumor recurrence n (%)	
No	168 (84.0%)
Yes	32 (16.0%)
Tumor differentiation n (%)	
intermediate	99 (49.5%)
Early	66 (33.0%)
Advanced	35 (17.5%)
Microvascular Invasion n (%)	
No	125 (62.5%)
Yes	75 (37.5%)
Recurrence free time median (IQR)	45.50 (17.00-79.00)
Recurrence time median (IQR)	12.00 (5.00-18.25)
Follow up time median (IQR)	56.00 (31.75-80.00)
Mortality time median (IQR)	11.50 (4.50-24.00)
N/L median (IQR)	2.67 (1.75-4.35)
APRI median (IQR)	1.49 (0.90-2.52)

contribution to the prediction of mortality and overall survival, their clinical utility in predicting tumor recurrence is limited due to their low PPV values. While studies showed that an increased APRI score predicts the risk of developing HCC in patients with chronic hepatitis B [13], the findings of studies investigating the relationship between a high APRI and HCC prognosis are inconsistent. Most of these were single-center studies and were limited to specific populations, such as hepatitis B-associated HCC or those following hepatectomy. We also eliminated liver fibrosis and cirrhosis, which are important risk factors for the development of HCC. We reflect the true outcome of the scoring system based on these factors. Our study is also consistent with the conclusion that a low fibrosis index after LT is a poor prognostic factor for HCC, as demonstrated in our previous study [14]. APRI, a marker associated with liver fibrosis, were found to be prognostic factors for OS in HCC patients, but were not statistically significant for RFS. Markers related to

inflammation and nutrition are known to be prognostic factors in HCC patients undergoing hepatic resection. Of these, high NLR is associated with poor outcomes [15], but whether it is a predictor of poor survival in HCC patients undergoing LT is unclear. We found that high NLR was a poor prognostic marker for OS. These results may be attributable to tumor pathogenesis, study population size, and the varying cutoff values used in previous studies. In our study, we demonstrated for the first time that APRI is an independent prognostic factor in HCC patients undergoing LT. Contrary to other studies, we analyzed whether high APRI levels are definitive predictors of poor survival. Our results showed that NLR and APRI were associated with high CP B and C, liver disease, including advanced cirrhosis, and high AFP reflecting aggressive tumors. Our multivariate results demonstrated that NLR and APRI scores, when combined with established prognostic factors such as MVI, tumor number and size, and AFP, can predict poor OS

Table 2. Univariate and multivariate COX regression analysis of factors associated with overall survival and recurrence-free survival

Overall Survival		Univariate			Multivariate	
Variable	p-value	HR	95% CI (Min-Maks)	p-value	HR	95% CI (Min-Maks)
Gender (men vs. female)	0.731	1.15	0.515 – 2.574	0.549	Oca.32	0.532 – 3.273
age	0.586	1.1	0.975 – 1.046	0.109	1.3	0.993 – 1.077
AFP	0.888	1.00	0.999 – 1.001	0.752	1.00	0.999 – 1.001
MVI	0.029	1.85	1.064 – 3.216	0.468	1.33	0.619 – 2.846
Locoregional treatment	0.728	1.11	0.607 – 2.043	0.732	0.88	0.432 – 1.804
Child-Pugh (general)	0.295			0.318		
Child-Pugh(B vs A)	0.510	1.23	0.665 – 2.274	0.882	1.6	0.490 – 2.296
Child-Pugh (C vs A)	0.120	2.19	0.816 – 5.858	0.161	2.43	0.702 – 8.412
MELD	0.944	1.00	0.954 – 1.045	0.765	1.1	0.949 – 1.074
size of HCC lesion(max)	0.002	1.2	1.006 – 1.027	0.067	1.1	0.999 – 1.028
number of HCC lesions	0.002	1.12	1.041 – 1.199	0.082	1.10	0.988 – 1.227
tumor differentiation (general)	0.437			0.690		
Tumor diff (early vs adv)	0.199	0.58	0.258 – 1.325	0.459	0.68	0.241 – 1.901
Tumor diff (interm. vs adv)	0.421	0.74	0.363 – 1.528	0.926	0.96	0.426 – 2.176
BMI	0.961	1.00	0.923 – 1.088	0.824	1.1	0.923 – 1.106
NLR (≤ 4.51 vs. > 4.51)	0.056	0.55	0.296 – 1.016	0.270	0.67	0.324 – 1.371
APRI (≤ 0.68 vs. > 0.68)	0.012	2.24	1.193 – 4.200	0.023	2.40	1.130 – 5.081
Recurrence Free Survival						
Gender (men vs. female)	1.000	1.000	0.406 – 2.467	0.536	0.647	0.163 – 2.567
age	0.958	0.999	0.966 – 1.033	0.300	1.028	0.976 – 1.082
AFP	0.905	1.000	0.999 – 1.001	0.338	0.999	0.997 – 1.001
MVI	0.686	1.213	0.477 – 3.083	0.913	1.085	0.251 – 4.696
Locoregional treatment	0.807	0.914	0.444 – 1.882	0.554	0.690	0.202 – 2.355
Child-Pugh (general)	0.126	1.824	0.845 – 3.936	0.401	1.807	0.454 – 7.203
Child-Pugh(B vs A)	0.991	0.993	0.288 – 3.428	0.115	0.138	0.012 – 1.623
Child-Pugh(Cvs A)	0.396	1.023	0.971 – 1.077	0.102	1.096	0.982 – 1.223
MELD	0.146	1.010	0.997 – 1.023	0.299	1.009	0.992 – 1.027
size of HCC lesion(max)	0.148	1.010	0.997 – 1.023	0.299	1.009	0.992 – 1.027
Number of HCC lesions	0.956	0.998	0.928 – 1.073	0.276	0.933	0.823 – 1.057
tumor differentiation(general)	0.118	0.435	0.153 – 1.235	0.060	0.235	0.052 – 1.062
Tumor diff (early vs adv)	0.856	1.083	0.458 – 2.559	0.248	0.493	0.148 – 1.639
Tumor diff (interm. vs adv)	0.230	0.934	0.836 – 1.044	0.902	0.989	0.826 – 1.183
BMI	0.373	1.078	0.914 – 1.270	0.838	1.183	0.236 – 5.935
NLR (≤ 4.51 vs. > 4.51)	0.196	0.528	0.201 – 1.391	0.345	0.477	0.
APRI (≤ 0.68 vs. > 0.68)	1.000	1.000	0.406 – 2.467	0.536	0.647	0.163 – 2.567

Table 3. Relationship between high and low NLR and APRI and demographic and tumor characteristics

	N/L ≤ 4.51 (n=154)	N/L > 4.51 (n=45)	p	APRI ≤ 0.68 (n=38)	APRI > 0.68 (n=161)	p
Gender n (%)						
male	126 (81.8%)	39 (86.7%)	0.508	30 (78.9%)	135 (83.9%)	0.477
female	28 (18.2%)	6 (13.3%)		8 (21.1%)	26 (16.1%)	
Age Median (IQR)	64.81 (57.73-72.61)	66.35 (59.41-70.14)	0.809	64.81 (57.73-72.61)	66.35 (59.41-70.14)	0.809
BMI Median (IQR)	26.00 (23.25-28.00)	27.00 (24.00-29.00)	0.282	26 (23.25-28)	27 (24-29)	0.282
diagnosis n (%)						
HBV	88 (57.1%)	24 (53.3%)	0.328	19 (50.0%)	94 (58.4%)	0.421
cryptogenic	17 (11.0%)	13 (28.9%)		6 (15.8%)	24 (14.9%)	
HCV	23 (14.9%)	3 (6.7%)		4 (10.5%)	22 (13.7%)	
ethanol	11 (7.1%)	2 (4.4%)		5 (13.2%)	8 (4.9%)	
nash	5 (3.2%)	2 (4.4%)		2 (5.3%)	5 (3.1%)	
budd-chiari	2 (1.3%)	1 (2.2%)		1 (2.6%)	2 (1.2%)	
wilson	2 (1.3%)	0 (0.0%)		0 (0.0%)	1 (0.6%)	
autoimmune	2 (1.3%)	0 (0.0%)		0 (0.0%)	2 (1.2%)	
HCC	2 (1.3%)	0 (0.0%)		0 (0.0%)	2 (1.2%)	
cholestasis	1 (0.6%)	0 (0.0%)		0 (0.0%)	1 (0.6%)	
hemochromatosis	1 (0.6%)	0 (0.0%)		1 (2.6%)	0 (0.0%)	
Child-pugh n (%)						
A	80 (51.9%)	14 (31.1%)	0.046	22 (57.9%)	71 (44.1%)	0.253
B	66 (42.9%)	27 (60.0%)		15 (39.5%)	79 (49.1%)	
C	8 (5.2%)	4 (8.9%)		1 (2.6%)	11 (6.8%)	
Meld Median (IQR)	9.50 (7.00-17.75)	12.00 (8.00-17.00)	0.170	9.5 (7.-17.75)	12 (8-17)	0.170
AFP Median (IQR)	3.60 (2.00-12.45)	11.00 (4.20-63.00)	0.001	3.6 (2-12.45)	11 (4.2-63)	0.001
Tumor size(mm) Median (IQR)	29.50 (11.75-40.00)	25.00 (17.00-43.00)	0.748	29.5 (11.75-40)	25 (17-43)	0.748
Number of HCC lesions Median (IQR)	2.00 (1.00-3.00)	2.00 (1.00-3.00)	0.691	2 (1-3)	2 (1-3)	0.691
Locoregional treatment n (%)						
No	107 (69.5%)	28 (62.2%)	0.369	26 (68.4%)	108 (67.1%)	1.000
Yes	47 (30.5%)	17 (37.8%)		12 (31.6%)	53 (32.9%)	
Mortality n (%)						
No	123 (79.9%)	30 (66.7%)	0.073	24 (63.2%)	129 (80.1%)	0.033
Yes	31 (20.1%)	15 (33.3%)		14 (36.8%)	32 (19.9%)	
Tumor recurrence n (%)						
No	129 (83.8%)	38 (84.4%)	1.000	32 (84.2%)	135 (83.9%)	1.000
Yes	25 (16.2%)	7 (15.6%)		6 (15.8%)	26 (16.1%)	
Tumor differentiation (%)						
intermediate	80 (51.9%)	18 (40.0%)	0.264	16 (42.1%)	83 (51.6%)	0.205
early	50 (32.5%)	16 (35.6%)		17 (44.7%)	48 (29.8%)	
advanced	24 (15.6%)	11 (24.4%)		5 (13.2%)	30 (18.6%)	
Microvascular Invasion n (%)						
No	96 (62.3%)	28 (62.2%)	1.000	26 (68.4%)	98 (60.9%)	0.459
Yes	58 (37.7%)	17 (37.8%)		12 (31.6%)	63 (39.1%)	
Recurrence free time Median (IQR)	35.00 (8.25-66.25)	55.00 (24.00-80.00)	0.017	35 (8.25-66.25)	55 (24-80)	0.017
Recurrence time Median (IQR)	12.00 (8.00-22.00)	12.00 (4.00-18.00)	0.424	12 (8.00-22.00)	12 (4-18)	0.424
Follow up time Median (IQR)	36.00 (14.25-66.25)	64.00 (36.00-81.00)	0.004	36 (14.25-66.25)	64 (36-81)	0.004
Mortality time Median (IQR)	15.00 (3.25-16.75)	11.00 (7.50-25.75)	0.867	15 (3.25-16.75)	11 (7.5-25.75)	0.867
N/L Median (IQR)	2.81 (1.54-4.84)	2.60 (1.75-4.30)	0.572	2.81 (1.54-4.84)	2.6 (1.75-4.3)	0.572
APRI Median (IQR)	0.42 (0.31-0.57)	1.70 (1.24-2.99)	<0.001	0.42 (0.31-0.57)	1.7 (1.24-2.99)	<0.001

and RFS before LT in patients with HCC. Tumor aggressiveness is closely related to surgical outcomes. Furthermore, NLR and APRI, both reflecting liver functional capacity and degree of fibrosis, have been shown to be important predictors of poor prognosis in patients undergoing surgery. Our study is a two-center study that included cirrhotic patients from diverse etiologies, encompassing a diverse population. In addition to the group of patients who did not receive preoperative

systemic therapy, it also did not include factors that could affect long-term outcomes after surgery, such as ablation, vascular interventional therapy, or molecular-targeting therapy. Systemic lymphocyte count indicates the recipient's cytotoxic immune response in HCC [16]. One of the main reasons for post-LT extrahepatic recurrences is that tumor cells escape immune surveillance with immunosuppressive therapy, which facilitates extrahepatic organ metastasis [17]. Serum albumin level is

one of the factors that plays a role in the immune response to tumor in addition to nutritional status [18]. NLR may affect surgery-related inflammation and the immune response in the transplanted graft in patients undergoing LT [19]. In parallel, a high NLR increases the risk of early complications, including tumor recurrence. This is associated with decreased survival and poor prognosis in the post-LT period [20]. According to these results, LT in patients with HCC should be individualized based on the clinical and pathological characteristics of the tumor, organ suitability, and the comparison of donor risk and recipient benefit expectations. Numerous HCC prognostic factors and models were identified in the past decades. Most of these were based on clinic-pathological, donor, and recipient factors [9,21]. NLR is one of the inflammation-related risk factors, reflecting both the antitumoral effect of the immune system and the systemic inflammatory state. Systemic inflammatory markers can be used to predict recurrence in high-risk patients. Neutrophils are classified according to their functional phenotypes in different inflammatory states. Although there are studies based on whether it promotes tumor progression or inhibits it due to the complex diversity [22]. However, NLR and APRI-based results

should be interpreted with caution because these biomarkers are influenced by several factors. Neoplasms such as HCC can influence the inflammatory and immune responses of patients [23]. Identifying a high-risk population by analyzing NLR and APRI in LT for HCC also constitutes a precise advantage in reducing failure-to-rescue.

Inflammatory parameters are reproducible, easy to perform, and cost-effective because they have very low variability even in complete blood counts that include different leukocyte types [24]. Complete blood count results and associated inflammatory markers could have been affected by acute rejection, immunosuppressive or systemic chemotherapy, and infections. However, HCC patients did not receive systemic therapy before LT, and surgery was not performed until the infection was controlled. Therefore, our results were not affected by these factors.

Limitations

To assess cutoff values for poor long-term survival, curve analysis of NLR and APRI may not be fully representative as this may not provide accurate long-term predictive value for LT outcomes. However, large-scale, multicenter studies would be beneficial to investigate better prognostic models for reducing postoperative recurrence and developing targeted therapies.

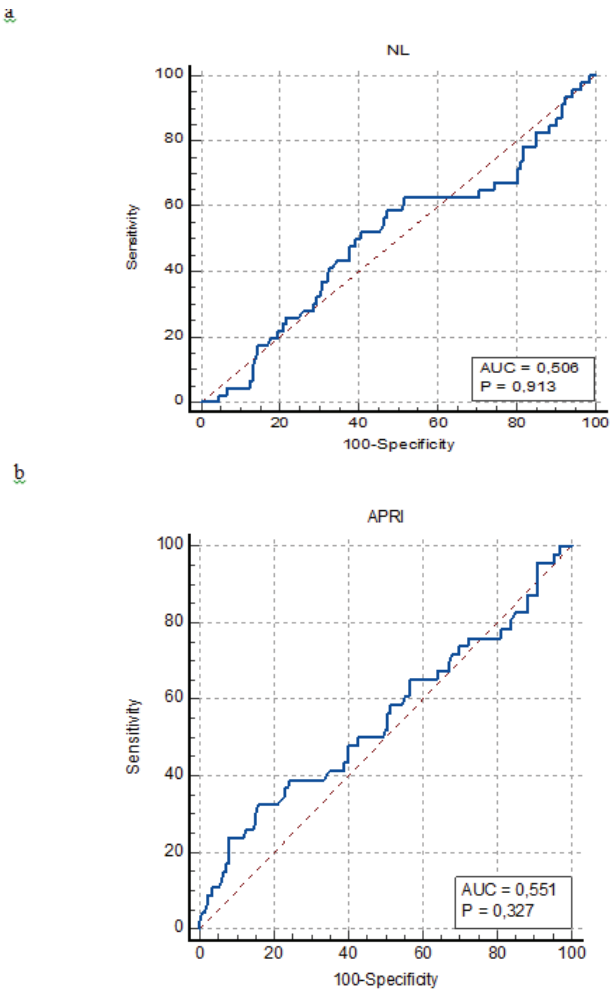


Figure 1. The Receiver Operating Characteristic (ROC) curves explore the value of preoperative NLR and APRI in predicting the long-term prognosis in Liver Transplantation (LT) for Hepatocellular Carcinoma (HCC). (a) The value of ROC in predicting overall survival in LT for HCC. (b) The value of ROC in predicting disease-free survival in LT for HCC

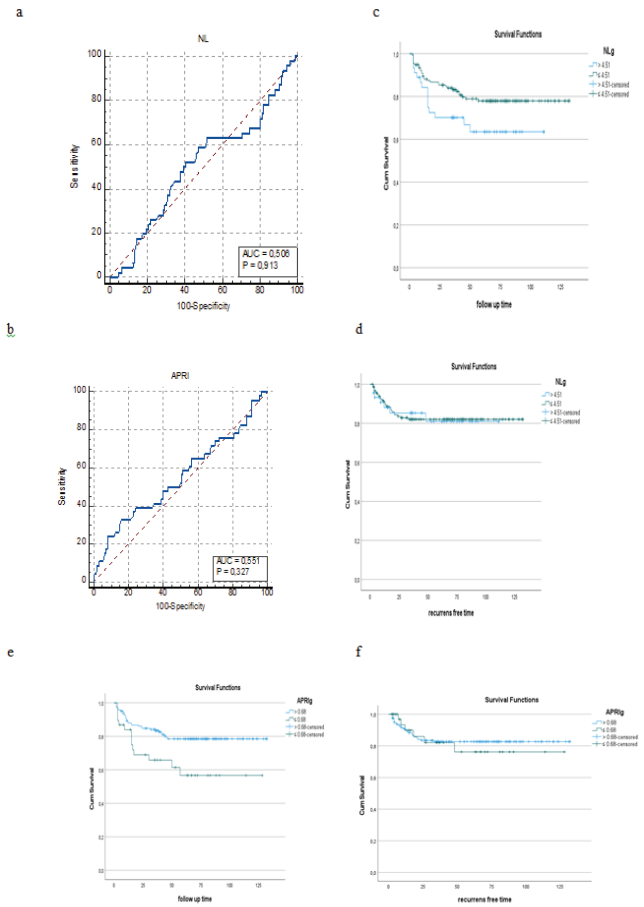


Figure 2. Receiver operating characteristic curve analysis of the preoperative NLR and APRI. a) 4.51 for the NLR b) 0.68 for the APRI. Overall and disease-free survival of patients after liver transplantation for HCC according to the NLR-APRI score in HCC patients from the entire cohort c) overall survival for NLR d) recurrence-free survival for NLR e) overall survival for APRI f) recurrence-free survival for APRI

Conclusion

Our study demonstrated the prognostic importance of inflammatory and fibrosis markers in patients with HCC undergoing LT. We demonstrated that low APRI and high NLR are associated with poor long-term outcomes in LT for HCC. The APRI score is an independent prognostic factor in HCC patients undergoing LT. NLR and APRI scores may be clinically helpful in making treatment decisions and predicting post-LT oncological outcomes in HCC patients. One of the limitation of this work is the retrospective nature of the data. They may affect the accuracy of the recorded biochemical and clinical parameters. According to these considerations, LT for HCC patients should be based on clinic-pathological characteristics, organ availability and the cost-benefit ratio of LT. Further research is needed to confirm the effectiveness of the markers as prognostic factor in HCC patients who underwent LT and to identify any interactions with other risk factors and outcome predictors.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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